FOLFIRINOX Therapy - (Rectal Carcinoma)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Neoadjuvant chemotherapy for locally advanced rectal cancer	C18	00691a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Treatment is administered every 14 days for 6 cycles unless progression or unacceptable toxicity develops. This is followed by 5 weeks of chemoradiotherapy.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Oxaliplatin[a]	85 mg/m^2	IV infusion	500mls 5% glucose over 2 hours immediately followed by:	Repeat every 14 days for 6 cycles
1	Folinic Acid[b] (Calcium leucovorin)	[c]400mg/m^2	IV infusion	250ml 0.9% NaCl over 2 hours with the addition after 30 minutes of irinotecan as below	Repeat every 14 days for 6 cycles
1	Irinotecan	180mg/m^2	IV infusion	250ml 0.9% NaCl over 90mins given through a Y connector placed immediately before the injection site Immediately followed by:	Repeat every 14 days for 6 cycles
1	5-Fluorouracil[d]	2400mg/m^2	Continuous IV infusion	Over 46 hours in 0.9% NaCl	Repeat every 14 days for 6 cycles

[a] Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline.
For oxaliplatin doses ≤ 104mg use 250ml glucose 5%.
Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction
Oxaliplatin administration must always precede the administration of 5-FU.

[b] Folinic Acid *(Calcium Leucovorin)* must be administered prior to fluorouracil. It enhances the effects of fluorouracil by increasing fluorouracil binding to the target enzyme thymidylate synthetase.

[c] A dose of 200mg/m^2 of folinic acid may be considered.

[d] See dose modifications section for patients with identified partial DPD deficiency.

Followed by:

Day	Drug	Dose	Route	Cycle
1-5	Capecitabine	800 mg/m^2 Twice daily[a,b,c,d]	PO	Every 7 days for 5 cycles with radiotherapy
[a] The dose to be administered should consider the available tablet strengths. Reference to the NCCP DOSE BANDING TABLES for dosing of capecitabine Here. Tablets should be swallowed whole with plenty of water with food or within 30 minutes of eating. Tablets should not be crushed or cut. [b] (total daily dose = 1600mg/m^2) [c] Consideration may also be given to the use of Capecitabine 825mg/m^2 twice daily as per NCCP Regimen 00586a at the discretion of the prescribing Consultant.				
[d] See dose modifications section for patients with identified partial DPD deficiency.				

ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Adequate haematological, renal and liver status.
  - Creatinine Clearance > 50ml/min

CAUTION:

Use with caution in patients with:

- Previous pelvic radiotherapy
- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)
- Symptomatic peripheral neuropathy
- In patients known to be homozygous for UGT1A1*28 consideration may be given to a reduced irinotecan starting dose

EXCLUSIONS:

- Hypersensitivity to irinotecan, oxaliplatin, 5-fluorouracil, capecitabine or any of the excipients
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Baseline neutrophils < 1.5 x 10^9/L and/or platelet count < 100 x 10^9/L
- Bilirubin > 3 x ULN
- Chronic bowel disease and/or bowel obstruction
- Pregnancy and lactation
- Severe bone marrow failure
- CNS metastases
- Known complete DPD deficiency
- Recent or concomitant treatment with brivudine

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- Blood, liver and renal profile
- ECG (if patient has compromised cardiac function)
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- Blood, liver and renal profile prior to each cycle
- Evaluate for peripheral neuropathy every cycle prior to proceeding with treatment

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Consider a reduced starting dose in patients with identified partial DPD deficiency.
    - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.
- Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction).
- Once the dose has been reduced, it should not be increased at a later time.
- For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption.
- Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs.
- Doses of capecitabine omitted for toxicity are not replaced.
- Any dose modification should be discussed with a Consultant.

Haematological

- Treatment is not administered unless ANC ≥1.5 x 10^9/L and platelets ≥100 x 10^9/L.
- If levels are below this at Day 1 treatment may be delayed for 1-2 weeks.
- If no recovery in 2 weeks consideration should be given to discontinuing the treatment.

Table 1: Dose modification of FOLFIRINOX based on Day 1 Absolute Neutrophil Count (ANC)

Adverse Event	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of ANC < 1.5 x 10^9/L	Reduce dose to 150mg/m^2	Maintain full dose	Maintain full dose
*2nd occurrence of ANC < 1.5 x 10^9/L	Maintain 150mg/m^2 dose	Reduce to 60mg/m^2	-
3rd occurrence ANC < 1.5 x 10^9/L	Discontinue	-	-

Table 2: Dose modification of FOLFIRINOX based on Day 1 Platelet Count

Adverse Event	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of platelets < 100 x10^9/L	Maintain full dose	Reduce to 60mg/m^2	Reduce continuous infusion dose by 25% (900mg/m^2/day)
2nd occurrence of platelets < 100 x10^9/L	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	-
3rd occurrence of platelets < 100 x10^9/L	-	Discontinue	-

Table 3: Dose modification of FOLFIRINOX based on low nadir blood counts or in case of infection

Adverse Event	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of • Febrile neutropenia • ANC < 0.5 x 10^9/L for > 7 days • Infection with concomitant ANC < 1 x 10^9/L	Reduce dose to 150mg/m^2	Maintain full dose	Maintain full dose
2nd occurrence of • Febrile neutropenia • ANC < 0.5 x 10^9/L for > 7 days • Infection with concomitant ANC < 1 x 10^9/L	Maintain 150mg/m^2 dose	Reduce to 60mg/m^2	Reduce continuous infusion to 2000mg/m^2
3rd occurrence • Febrile neutropenia • ANC < 0.5 x 10^9/L for > 7 days • Infection with concomitant ANC < 1 x 10^9/L	Discontinue treatment		
1st occurrence of Platelets < 50x 10^9/L	Maintain full dose	Reduce to 60mg/m^2	Maintain full dose
2nd occurrence of Platelets < 50x 10^9/L	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	Reduce infusional dose by 25%
3rd occurrence of Platelets < 50x 10^9/L	Discontinue treatment		

*For any febrile neutropenia or a 2nd episode of ANC < 1x10^9/L. G-CSF prophylaxis should be considered for subsequent cycles.

Renal and Hepatic Impairment:

Table 4: Recommended dose modifications for patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment
Oxaliplatin	**CrCl (ml/min)**	**Dose**	Little information available. Probably no dose reduction necessary. Clinical decision.
	>30	Treat at normal dose and monitor renal function	
	<30	Contraindicated	
Irinotecan	No dose reduction needed, however use with caution as no information in this setting.		Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN.
5-Fluorouracil	Consider dose reduction in severe renal impairment only		**Bilirubin (micromol/L)** / **AST** / **Dose** <85 / <180 / 100% >85 or >180 / Contraindicated Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. Increase dose if no toxicity.
Capecitabine	**Cr Cl (ml/min)**	**Dose**	In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis.
	≥ 50	100% dose	
	< 50	75% dose	
	< 30	Discontinue treatment	

Management of adverse events:

Table 5: Dose Modifications for Oxaliplatin* NEUROLOGICAL Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1-7 days	> 7 days	
1	Maintain dose level	Maintain dose level	Maintain dose level
2	Maintain dose level	Maintain dose level	↓ 1 dose level
3	65mg/m^2	65mg/m^2	Discontinue therapy
4	Discontinue therapy		
Laryngo-pharyngeal dysaesthesia	Maintain dose level. Increase infusion time from 2 to 6 hrs		
***If oxaliplatin is discontinued due to neurotoxicity, irinotecan and 5-fluorouracil are continued**			

Table 6: Dose modification schedule based on non-haematological, non-neurological toxicities

Adverse Event	Irinotecan	Oxaliplatin	5-Fluorouracil
Grade 3-4 diarrhoea OR Diarrhoea, fever and/or ANC < 1 x 10^9 /L			
• 1st occurrence	Reduce dose to 150mg/m^2	Maintain full dose	Maintain full dose
• 2nd occurrence	Maintain dose at 150mg/m^2	Reduce dose to 60mg/m^2	Reduce continuous infusion by 25% to 900mg/m^2/day
• 3rd occurrence	Discontinue	-	-
Persistent diarrhoea (>48h) despite high doses of loperamide	No reduction in irinotecan or oxaliplatin or 5-FU dose after recovery **unless** grade 3-4 diarrhoea, or diarrhoea + fever and/or grade 3-4 neutropenia		
Mucositis or "hand foot" syndrome Grade 3 or 4			Reduce continuous infusion by 25% to 900mg/m^2/day for subsequent cycles

Elevation of Bilirubin:

Elevation of bilirubin should be investigated to determine the cause and the dose of irinotecan should be adjusted if medically indicated.

Table 7: Dose modification schedule based on elevated bilirubin

Bilirubin	Dose reduction at next cycle
27-50 micromol/L	Reduce the irinotecan dose to 50%
>50 micromol/L	Stop irinotecan

Table 8: Dose modification of capecitabine due to toxicity

Toxicity NCI Grade	Discontinuation of capecitabine	Modification of dose
Grade 1	No	No
Grade 2 1st episode	Hold treatment until resolves to grade 0-1	Reduce dose to 600mg/m^2 twice daily
Grade 2 2nd episode	Hold treatment until resolves to grade 0-1	Reduce dose to 400mg/m^2 twice daily
Grade 2 3rd episode	Hold treatment until resolves to grade 0-1	
Grade 3	As for grade 2	
Grade 4	Definitive discontinuation or hold until resolves to grade 0-1	
Angina, infarction	Definitive discontinuation	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: This regimen poses an overall high risk of emesis

5-Fluorouracil: Low (**Refer to local policy).**
Irinotecan: Moderate (**Refer to local policy).**
Oxaliplatin: Moderate (**Refer to local policy).**
Capecitabine: Minimal to low **(Refer to local policy).**

PREMEDICATIONS:

Prophylactic atropine sulphate 250micrograms subcutaneously – see adverse effects below.
Atropine should not be used in patients with glaucoma (See Adverse Effects/Regimen specific complications below).

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment **(Refer to local policy).**
Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of irinotecan and at any time before the next cycle.

- As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate anti-diarrhoeal therapy must be initiated immediately.
- The currently recommended anti-diarrhoeal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours).
- This therapy should continue for 12 hours after the last liquid stool and should not be modified.
- In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Diarrhoea and dehydration** is associated with the use of both Irinotecan and capecitabine. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Irinotecan-induced diarrhoea can be life threatening and requires immediate management.
    - Diarrhoea (early onset) - see acute cholinergic syndrome above.
    - Diarrhoea (late onset):
    - Irinotecan induced diarrhoea can be life threatening and requires immediate management.
    - In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan.

- Patients with an increased risk of diarrhoea are those who had previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women.
- In patients who experience severe diarrhoea, a reduction in dose is recommended for subsequent cycles.
- The SmPC (6) provides guidelines on when hospitalisation for the management of diarrhoea is recommended.

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with fluorouracil and capecitabine. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency**: DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.
- **Hand-foot syndrome (HFS):** HFS, also known as palmar-plantar erythrodysaesthesia (PPE), has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil and capecitabine.

Oxaliplatin

- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysaesthesia:** An acute syndrome of laryngopharyngeal dysaesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.
- **Gastrointestinal toxicity:** It manifests as nausea and vomiting and warrants prophylactic and/or therapeutic anti-emetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5FU.
- **Extravasation:** Oxaliplatin causes irritation if extravasated **(Refer to local policy).**
- **Venous occlusive disease:** A rare but serious complications that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.

- **Haemolytic Uraemic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

Irinotecan

- **Acute cholinergic syndrome:** If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation) atropine sulphate (250 micrograms subcutaneously) should be administered unless clinically contraindicated. Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan**.**
- **Extravasation:** Irinotecan causes pain and tissue necrosis if extravasated **(Refer to local extravasation guidelines).**
- **Gilbert's Syndrome:** Increases the risk of irinotecan-induced toxicity. A reduced initial dose should be considered for these patients.
- **Respiratory disorders:** Severe pulmonary toxicity has been reported rarely. Patients with risk factors should be monitored for respiratory symptoms before and during irinotecan therapy.

DRUG INTERACTIONS:

- Risk of drug interactions causing decreased concentrations of irinotecan with CYP3A inducers.
- Risk of drug interactions causing increased concentrations of irinotecan with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity. Capecitabine enhances the anticoagulant effect of warfarin. Patients taking coumarin derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anti-coagulant dose adjusted accordingly.
- Sorivudine inhibits dihydropyrimidine dehydrogenase thus increasing its toxicity. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Current drug interaction databases should be consulted for more information.

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1	30/03/2022		Prof Maccon Keane
2	05/09/2022	Updated emetogenic potential	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.